PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**(MBHB Case No. 04-1028-B)**

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| In re Application of: Druzgala et al. | ) | |
| | ) | Group Art Unit: 1743 |
| Serial No.: 10/643,699 | ) | |
| | ) | Examiner: Kantamneni, Shobha |
| Filed: August 18, 2003 | ) | |
| | ) | Confirmation No.: 5094 |
| For: Materials and Methods for the Treatment of Hypertension and Angina | ) | |

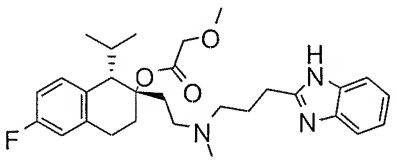
**PRE-APPEAL BRIEF**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

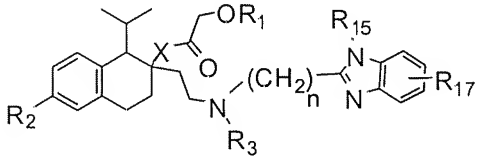
Dear Sir:

Applicants request review of the Office Action mailed July 18, 2006 because the Examiner, when responding to Applicants' arguments, made errors in law.

The instant claims are directed to a method for blocking a calcium channel in a patient comprising administering a compound of the instant invention. Compounds of the instant invention, as previously presented in Applicant's Response mailed July 18, 2006, are structurally similar to Mibefradil, a well-known calcium channel inhibitor. The structure of Mibefradil and compounds of the instant invention follow:

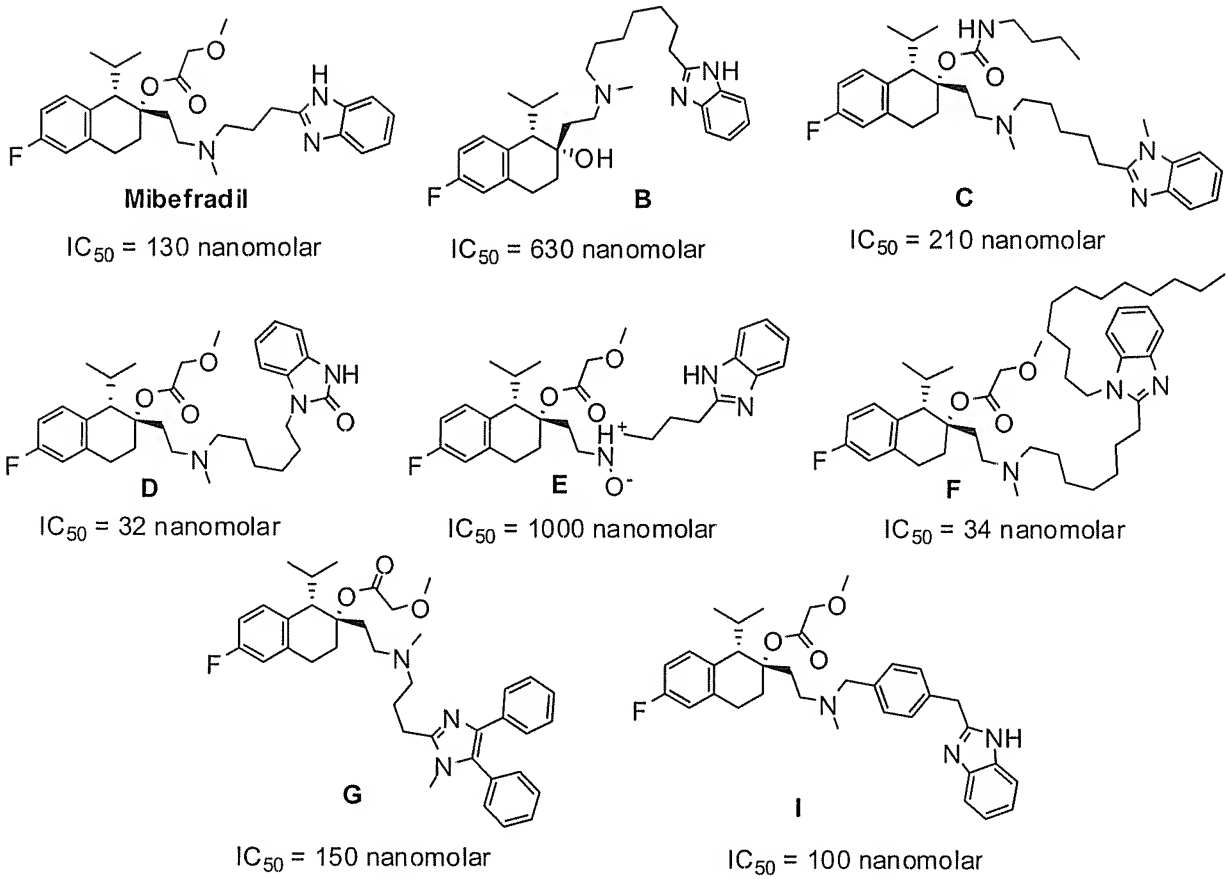


**Mibefradil**



Claim 23 n=1-6

Further, it is well-known in the art that Mibefradil analogs block calcium channels. As an example, US 4808605 ('605) provides calcium channel inhibitory data for Mibefradil and analogs thereof:




The '608 data demonstrates calcium channel blocking efficacy for Mibefradil analogs substituted with either lipophilic or polar groups.

The Examiner rejected method of treatment claims 23-29 and 32-34 for allegedly lacking enablement under 35 U.S.C. § 112 first paragraph. The Examiner asserts that the "specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation." Applicants respectfully submit that the Examiner made an error of law in not fully considering what is well-known in the art. The MPEP provides:

> "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art."
> MPEP 2164.01 citing *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) (emphasis added).

The specification, when coupled with what is well-known in the art, enables one reasonably skilled in the art to make or use the instant invention.

Further, the Examiner asserts in the undue experimentation analysis that:

(1) "[t]he complex nature of the subject matter...is greatly exacerbated by the breadth of the claims[;]"

(2) "the claimed invention is highly unpredictable" with regard to:

(i) calcium channel blocking ability;

(ii) enzymatic hydrolysis; and

(iii) drug-drug interactions;

(3) "[l]ack of a working example is a critical and crucial factor...especially in a case involving an upredictable and undeveloped art[;]" and

(4) "[i]n order to practice the invention" one skilled in the art has to:

(i) "envision a specific soft calcium channel blocking compound;"

(ii) envision "a dosage for each compound;"

(iii) envsion "the duration of treatment;"

(iv) envison the "route of administration;"

(v) "determine whether...the compound is effective;" and

(vi) "test the compound...for side effects and toxicity."

Applicant's Response mailed July 16, 2006, pages 8-12 and 12-13, addresses the Examiner's assertions in (1) and (3) respectively.

Again, applicants respectfully submit that the Examiner made an error in law by not fully considering the state of the art with regard to assertions (2)(i), (3), (4)(i), and (4)(v) above. One reasonably skilled in the art can predict that the instant compounds inhibit calcium channels based on their structural similarity with Mibefradil and the '608 analogs.

With regard to assertion (2)(ii), applicants submit that the Examiner made an error of law by not fully considering the state of the art. It is well-known in the art that esters are hydrolyzed by a variety of nonspecific esterases in liver, plasma, gastrointestinal tract, and other tissues. *Goodman and Gillman's The Pharmacological Basis of Therapeutics* 21 (7th ed., MacMillan Publishing Company 1985). The instant compounds contain an ester substituent, therefore, one reasonably skilled in the art can predict enzymatic hydrolysis as a metabolic route for

compounds of the instant invention.

The remaining assertions directed to drug-drug interactions, dosage determination, duration of treatment, route of administration, and testing for side effects/toxicity are the province of the Food & Drug Administration, not the PTO. Applicants respectfully submit that the Examiner made an error in law by considering these factors in the undue experimental analysis. The MPEP provides:

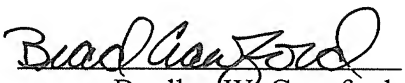
> "...it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained with-out undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use with-out undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The application need not demonstrate that the invention is completely safe." MPEP 2164(c).

Applicant's Response mailed July 18, 2006 at pages 13-14 further addresses the Examiner's error in law.

For the foregoing reasons, Applicants submit that the outstanding rejection of Claims 23-29 and 32-34 should be withdrawn.

Respectfully submitted,

Date: Jan. 11, 2007

By: 

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